REMARKS

Responsive to the Office Action mailed January 25 and with an extension of time of THREE MONTHS, the present paper is timely filed on or before July 25, 2006. By the present paper, claims 11 and 16 are amended and no claims are cancelled. Accordingly, claims 11 - 18 are presently under examination.

Applicants acknowledge with gratitude the recitation in the Office Action that claim 17 contains patentable subject matter. Applicants defer rewriting claim 17 until the patentability of the remaining claims under examination is finally determined.

The Claim Amendments:

Claim 16 is amended to recite that toluene, an aromatic hydrocarbon, is the 'first solvent' recited in claim 15, from which claim 16 depends. Applicants respectfully submit that support for the amendment can be found in the specification at, for example, page 3, line 16.

Claim 11 is amended to include the limitations of withdrawn claim 1 from which it depended. Applicants respectfully submit that support for the amendments can be found in the specification as filed.

Applicants further respectfully submit that the amendments do not introduce new matter into the application.

Claim Rejections Under 35 U.S.C. § 112, Paragraph Second:

Claim 16 was rejected under 35 U.S.C. § 112, ¶2 as allegedly indefinite. Applicants respectfully submit that the present amendments to claim 16 render to rejection moot and that the rejection should therefore be withdrawn.

Claim Rejections Under 35 U.S.C. § 103(a):

Claims 11 - 16 and 18 were rejected as allegedly obvious over Anderson et al., WO 99/388847 (Anderson et al.) in view of Le Bordonnec et al., J. Med. Chem. 43, 2685-97 (2000) (Le Bourdonnec et al.) because, relying on *In re Durden*, 763 F.2d 1406; 226 U.S.P.Q. 359 (Fed. Cir 1985), it is alleged that Applicants merely claim use of 'analogous reactants' in

a known process. Because Applicants invention, *viewed as a whole*, is not obvious in view of the applied art, Aplicants respectfully traverse.

Applicants respectfully point out that the issue in *Durden* was narrowly framed in that *Durden* rested the patentability of the claimed process on the patentability of the reactants, *Durden* at 360. Furthermore, the Federal Circuit expressly declined to establish a *per se* rule in this 'analogous reactant' scenario. *Durden* at 362. Nothing in *Durden* can be taken to alter the basic test for obviousness established by the Supreme Court in *Graham v. John Deere. Graham v. John Deere Co.,* 383 U.S. 1 (1966).

Furthermore, in at least three instances, the Board of Patent Appeals and Inteferences has called into doubt or refused to extend *Durden*. *Ex Parte Paul J. Reider and Edward J. Garabowski,* Appeal 95-3156 (Bd. Pat. App. & Interfer. 1995); *Ex Parte Cherylyn Lee and Larry F. Charbonneau*, Appeal 95-2142 (Bd. Pat. App. & Interfer. 1995); *Ex Parte Tse W. Chang and Nancy T. Chang*, Appeal 93-3529 ((Bd. Pat. App. & Interfer. 1993). Rejection of a process claim as obvious *per se* merely because the reactants are analogous to those in a known reaction ignores the requirement that a claimed invention be viewed as a whole and, in the extreme, would require, for example, rejection of any claim to an S_{N2} reaction as obvious because SN2 reactions are known and, mechanistically speaking, analogous; or of all reactions that use a phase transfer catalyst simply because the availability of phase transfer catalysts is generally known.

Applicants' claim 11 is reproduced below (formatting added to assist reading).

> A method for making irbesartan comprising the steps of:
> ~~preparing 2-butyl-3-[2'-(triphenylmethyltetrazol-5-yl)-biphenyl-4-yl methyl]-1,3-diazaspiro[4.4]non-1-ene-4-one prepared according to the method of claim 1~~;
> combining 2-butyl-1,3-diaza-spiro[4.4]non-1-ene-4-one and 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1*H*-tetrazole in the presence of a phase transfer catalyst in a reaction system comprising first and second phases;
> heating the combination to a temperature of about 20° C and about 95° C;
> separating the first and second phases; removing solvent from the first phase to obtain a residue;
> providing a mineral or sulfuric acid acidified solution of the residue in a water-miscible solvent,
> basifying the solution in water-miscible solvent with an inorganic base;
> removing water-miscible solvent from the solution;

separating trityl alcohol so formed;
and recovering irbesartan.

Claim 11, read in its entirety, includes 7 elements or limitations and is limited to a method of making irbesartan. Applicants respectfully submit that the applied art, alone or in combination, does not teach or suggest all of the claim limitations.

Anderson et al. teaches a method of making irbesartan that includes the step of reacting a bromomethyl cyano biphenyl, not 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1*H*-tetrazole as expressly required by claim 11, with 1,3-diazaspiro[4.4]nonan-4-one HCl. The reaction is carried out in a volatile organic solvent in the presence of a phase transfer catalyst.

The Office makes the naked allegation that a cyano reactant and a triphenyltetrazoyl reactant are 'analogous'. Applicants respectfully submit that the Office must supply at least some technical reasoning as to why the skilled artisan of the day would have expected that cyano compound and a tetrazoyl compound could have been freely interchanged, particularly in view of the fact that Anderson et al. discloses that the nitrile compound is preferred. Anderson et al. at page 1, line 27.

The Office attempts to overcome this deficiency in analysis by combining Le Bourdonnec et al. with Anderson et al. But this combination fails because Le Bourdennec et al. is directed to a structurally different class of compounds, namely pyrazolidine-3,5-diones.

The starting materials in the process disclosed in Le Bourdonnec et al. therefore do not contain the imidazol-4-one ring which is present in the reactants in Applicants' inventive process. This structural difference means that the compounds have very different reactivities. For example, in the alkylation step in Scheme 2 on page 2687 of Le Bourdonnec et al. (i.e. step a or step b), the spiro intermediates (Compounds 4-6 and 15) contain only a single free -NH group that can be alkylated because the second nitrogen is protected by an 'R' group. In Applicants' inventive process, the starting material contains two alkylateable nitrogens. Applicants respectfully submit that, in view of these diffecrences, the Office has not presented any explanation as to why a person of skill in the art would have considered that the disclosure of Le Bourdonnec et al. could be applied or adapted to the teachings of Anderson et al.

Moreover, even if, *arguendo*, the skilled person would have considered applying the teaching of Le Bourdonnec et al. to make irbesartan, he would not arrive at all of the limitations of the claimed process. According to Scheme 2 on page 2687 of Bourdonnec et

al., two different processes to the AT_1 ligands (compounds 25-28) are disclosed; namely:

Process (1) = steps a and d
Process (2) = steps b and c

Process (2), i.e. steps b and c, is in fact, taught only for those compounds wherein the R substituent contains a phenyl or an alkylvhenyl group (compounds 25, 26, and 27 in Le Bourdonnec et al.). Thus, for these compounds, Le Bourdonnec et al. teaches reacting the spiro intermediate - compounds 4-6, in which the group R is one of C_6H_5, $C_6H_4CH_3$(p) or $CH_2C_6H_5$ - with the tetrazole intermediate 19. The resulting trityl-substituted products (i.e. compounds 20-22) are subsequently deprotected to form the final compounds 25-27.

Process (1) of Le Bourdennec et al , i.e. steps a and d, involves reaction of the spiro intermediate 15, wherein R is butyl, to form the carbonitrile intermediate 24, which is subsequently converted to the tetrazole substituted final product 28. Thus, Le Bourdonnec et al. cannot be said to suggest, let alone teach, reation *via* the tetrazole intermediate 19, even for the structurally closest analogue to irbesartan (the compound wherein R is butyl). Rather, for the compound wherein R is butyl, Le Bourdonnec et al. specifically teaches proceeding via the carbonitrile intermediate 24 (see also page 2687. left hand column. lines 19-23). There is no suggestion whatsoever in Le Bourdonnec et al. to apply the process involving steps b and c to a butyl-substituted intermediate.

There is no teaching or suggestion to combine Le Bourdennec et al. Anderson et al. and, even *if* combined, the references do not teach or suggest Applicants' process, as a whole, as Applicants claim it. Accordingly, Applicants respectfully submit that the rejection of claim 11 is improper and should be withdrawn. Because, as Applicants respectfully submit, claim 11 contains patentable subject matter, claims 12 - 14 likewise contain patentable subject matter and Applicants respectfully submit that the rejectiopn of these claims should likewise be withdrawn.

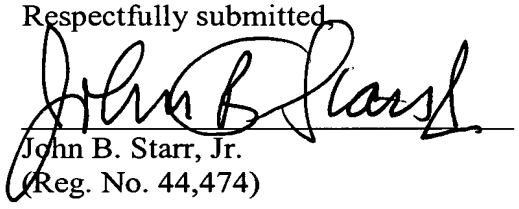
For the reasons stated above in discussion of the rejection of claim 11, Applicants respectfully submit that the rejection of claim 15 and claims 16 and 18 that depend therefrom should be withdrawn.

Conclusion:

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the claims are now in condition for allowance, which allowance is earnestly solicited. If, in the opinion of the Examiner, a telephone conference would advance prosecution of the Application, the Examiner is invited to telephone the undersigned attorney.

Dated: July 25, 2006

Respectfully submitted,



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